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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,348	07/13/2001	Avi Ashkenazi	10466/55	3826

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EXAMINER

SAOUD, CHRISTINE J

ART UNIT PAPER NUMBER

1647

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,348	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44-46 and 49-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-46 and 49-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

Claims 44-46 have been amended as requested in the paper filed 09 August 2004 (and 06 December 2004). Claims 44-46 and 49-51 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 09 August and 06 December 2004 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 44-46 and 49-51 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons of record in the previous Office actions.

Applicant's arguments (submitted in the after-final response of 09 August 2004 and in the instant response) have been fully considered but are not found to be persuasive for the following reasons. The Polakis declaration under 37 CFR 1.132 filed 09 August 2004 is insufficient to overcome the rejection of claims 44-46 and 49-51 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons.

At page 5 of the response, Applicant argues that the Haynes et al. publication does not support the rejection. Applicant characterizes Haynes et al. as teaching that there is a general trend but no strong correlation between polypeptide expression level and transcript level. Applicant criticizes Haynes et al. for being directed to a study of yeast polypeptides. Applicant further characterizes Haynes et al.'s conclusions as showing that there is a positive correlation between transcript and polypeptide for most of the 80 yeast polypeptides studied, but the correlation is not linear and thus one cannot accurately predict polypeptide levels from mRNA levels. Applicant stresses that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and polypeptide. Applicant concludes that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO232. There is no evidence regarding whether or not the PRO232 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Since the instant claims are directed to PRO232

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polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and polypeptide levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Konopka et al. was cited as evidence showing lack of correlation between gene amplification and increased polypeptide levels. Haynes et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO232 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. One skilled in the art would do further research to determine whether or not the PRO232 polypeptide levels increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the

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public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done

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for PRO232 in the instant specification. That is, it is not clear whether or not PRO232 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO232 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to

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approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO232 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 44-46 and 49-51 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer

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samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants further assert that even if one assumes that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility, and provides the declaration by Dr. Avi Ashkenazi (filed 10 December 2003 and already considered in a previous Office action). Dr. Ashkenazi explains that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not-overexpressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product

The declaration filed under 37 CFR 1.132 filed 10 December 2003 is insufficient to overcome the rejection of claims 44-46 and 49-51 based upon lack of utility as set forth in the previous Office actions because: it has not been demonstrated that the

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protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician would accordingly decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product.

Applicants provide the Hanna et al. reference to support the Declaration of Dr. Ashkenazi. The Hanna reference is not applicable to the instant fact situation, as it deals with a known tumor associated gene, and not with a prospective analysis of the type found in this specification.

For all of these reasons, the rejections are maintained.

Claims 44-46 and 49-51 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific

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and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Priority Determination

As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. §§ 101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 13 July 2001.

Claim Rejections - 35 USC § 102

Claims 44 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenthal et al. (DE 19818619-A1, 28 October 1999) for the reasons of record in the previous Office actions .

Applicant argues that the claimed priority of the instant application is 17 September 1997, and therefore, the rejection is not proper. This argument is not persuasive in light of the utility rejection and the effective priority of the instant application based on lack of utility.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on mtrr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud